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The therapy of chronic pouchitis

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Ulcerative colitis (UC) is an inflammatory bowel disease characterized by inflammation restricted to the large bowel mucosa. Up to one-quarter of patients with UC will eventually undergo total proctocolectomy.[1]

Since the first description by Parks in 1978, ileal pouch-anal anastomosis (IPAA) has become the surgical procedure of choice for both UC refractory to medical therapy and in those who develop colonic dysplasia or cancer and familial adenomatous polyposis (FAP).[2]

Since UC is primarily restricted to the large bowel, it was expected that IPAA will enable eradication of diseased and cure the UC. However, following the surgery up to 30% may develop chronic pouchitis.[3]

Pouchitis is clinically characterised by symptoms that include increased stool frequency, haematochezia, abdominal cramping, urgency, tenesmus, incontinence, fever and extraintestinal manifestations.

Pouchitis is a nonspecific inflammatory condition in the ileal pouch reservoir.[4] The fact that pouchitis occurs more commonly in those who have a pouch for UC than for FAP suggests that both the immune system and its regulation have a role in the aetiology. Some evidence suggests that an abnormal mucosal immune response to altered microflora in the ileal pouch leads to inflammation.

The diagnosis of pouchitis has no standard definition. The most commonly used criterion is the pouch disease activity index (PDAI). The PDAI is a composite score including clinical symptoms, endoscopic findings and histological findings. A score greater than 7 is required for a diagnosis of pouchitis. Differential diagnosis of pouchitis include pouch ischemia, pouch stenosis, impaired pouch emptying, infectious diarrhea such as cytomegalovirus or clostridium difficile, Crohn's disease (CD) of the pouch, adhesions.

Controversy remains about anal and vaginal fistulas in patients with a pouch and what they represent. It

is possible that some of these are due to CD, whereas others are caused by underlying pelvic sepsis, surgical complication or cryptoglandular sepsis distinct from CD.[5]

Although the majority of patients with pouchitis respond favourably to antibiotic therapy, particularly in the initial stage of the disease, in the longer term, in many patients pouchitis becomes refractory to conventional antibiotic therapy. In practice, antibiotics are often needed to maintain symptomatic response and symptoms return on withdrawal.

Chronic pouchitis has no standard definition, but is often defined as the need for antibiotics for greater than 4 weeks with evidence of pouchitis.[6] Chronic pouchitis develops in approximately 5%-19% of patients who either become dependent on antibiotics for symptom relief or have symptoms refractory to conventional therapies.[7]

Regarding primary prophylaxis of pouchitis, a low-carbohydrate, low-fibre, and high-protein diet is recommended at baseline. In a randomized trial of 40 consecutive patients who underwent IPAA were given either probiotic therapy with VSL#3, 1 packet (900 billion bacteria including Lactobacillus species, Bifidobacterium supplementation, *Streptococcus salivarius* supplementation, and Thermophilus supplementation) each day or placebo for 12 months after ileostomy closure. VSL#3 reduced the incidence of acute pouchitis—only 10% of patients that received VSL#3 (2/20) developed pouchitis, while 40% of the placebo group (8/20) developed pouchitis ($P < 0.05$).[8]

The first-line treatment of acute pouchitis is empirical with antibiotics. Ciprofloxacin and metronidazole are the most commonly used, often generating a rapid dramatic response after a 2- to 4-week course (70% of remission), with rifaximin and tinidazole being alternative agents to try in combination. Long-term use of antibiotics is poorly effective in achieving clinical remission for those patients with chronic pouchitis, but may be useful at keeping symptoms under control.[9]

Patients with antibiotic-refractory pouchitis may need to opt for salicylates, corticosteroids (i.e.

budesonide), immunosuppressive drugs (i.e. azathioprine), or anti-TNF biologics.

Treatment of a recurrent episode of pouchitis should first be directed toward a repeat trial of antibiotics or a trial of combination antibiotic therapy.

Patients who continue to have relapses of pouchitis despite antibiotics at least 3 times each year are considered to have a chronic antibiotic-dependent pouchitis. These patients often require rotating courses of antibiotics, and these patients should also be placed on maintenance therapy.

A randomized controlled trial of 40 patients given 2 packets/day of VSL#3 (600 billion bacteria) or placebo showed that VSL#3 was able to prevent a relapse during the study follow-up period of 9 months (15% of VSL#3 had relapse vs 100% placebo, $P < 0.001$).[8]

Oral budesonide is used at 9 mg/day for 3 months, then 3–6 mg/day for maintenance. Steroid therapy with budesonide has been tried in multiple small studies with reported remission rates of 60%–75%. Another steroid, beclomethasone diproprionate, was tried in an open-label study of 10 patients for 8 weeks, and 80% of patients achieved remission based on a total PDAI < 4.[10]

Topical mesalazine has been given to patients with pouchitis with clinical and endoscopic improvement.

Immunosuppression with immunomodulators such as azathioprine or 6-mercaptopurine has also been used by some providers, although little data exists regarding the use of immunomodulator monotherapy for pouchitis.

Studies including small numbers of patients (often fewer than 20), and mostly retrospective in design have demonstrated that infliximab appears to have good clinical effectiveness in selected patients with pouchitis, achieving up to 80% short-term and around 50% long-term response. Some data suggest that potentially, in some patients started on anti-TNF medications for pouchitis, we may be delaying

inevitable surgery rather than having a meaningful impact on disease course.[11]

In an open-label, prospective, single arm, multicentre study was evaluated the efficacy of granulocyte and monocyte apheresis in patients that had active pouchitis while on conventional medical therapy including corticosteroids, amino-salicylates and anti-TNF biologics in addition to antibiotics. Nearly half of the patients (46%) responded to the treatment, but without achieving complete remission.[12]

In a case series of 5 patients receiving multiple faecal microbiota transplantation (range 1–7) via flexible sigmoidoscopy had symptom resolution in 80% (4/5) within 4 weeks, and 75% (3/4) of the responders remained in remission for 3 months.[13]

Finally, case series about emerging role of vedolizumab or ustekinumab as a treatment option for chronic have been published.[14,15]

In conclusion, treatment of chronic refractory pouchitis remains an unmet need of UC' management.

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